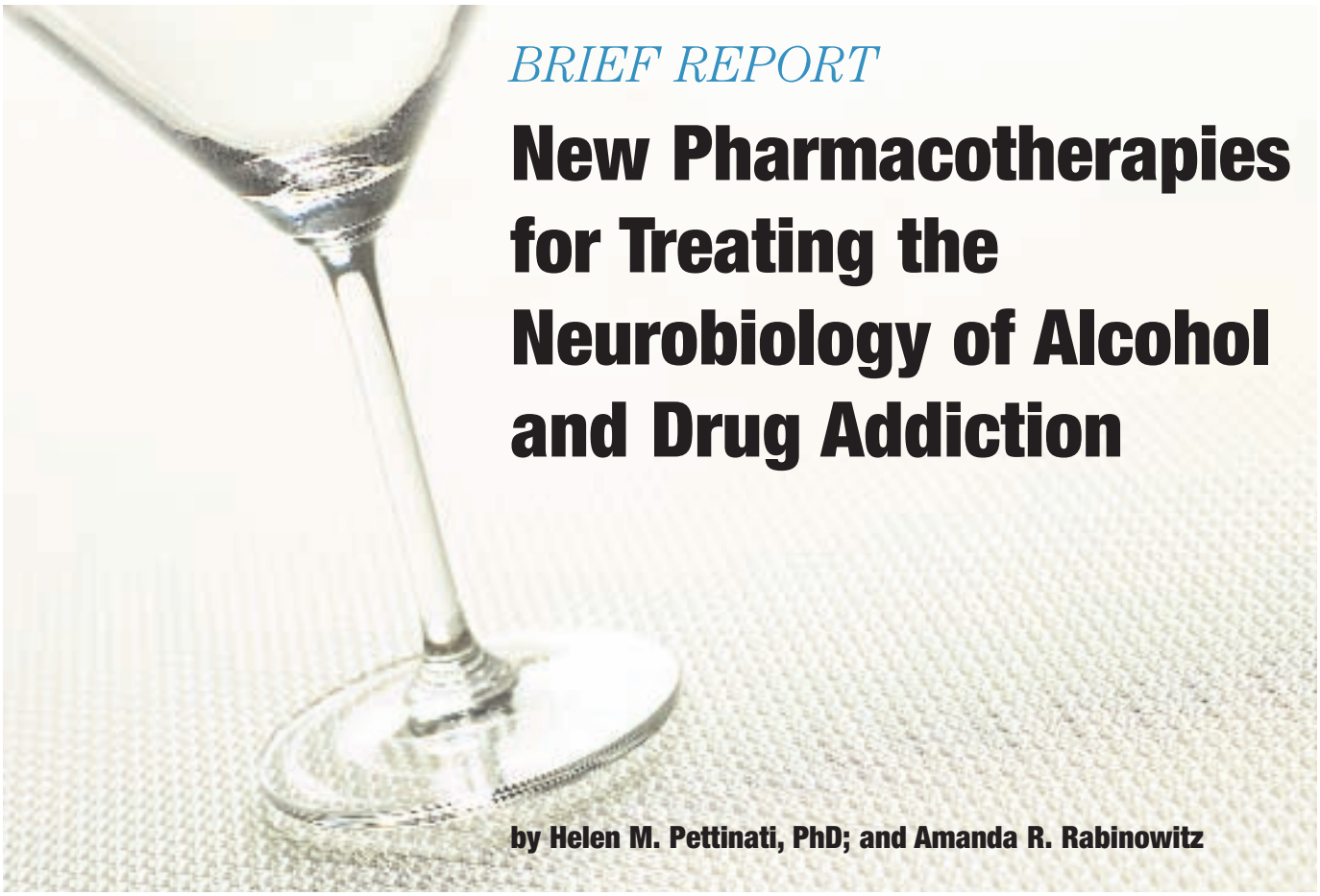

BRIEF REPORT

New Pharmacotherapies for Treating the Neurobiology of Alcohol and Drug Addiction

by Helen M. Pettinati, PhD; and Amanda R. Rabinowitz

In the past decade, scientists have made important progress toward understanding the neurobiology underlying drug and alcohol addiction. This knowledge has led to the development of promising phamacotherapies that target the neural pathways involved in the brain's reward center in such a way that the usual treatment response (via counseling) is substantially improved upon. Today there are some FDA-approved options, for example, for treating cigarette smoking as well as alcohol disorders—with a number of medications under development by NIH or by pharmaceutical companies for treating these addictions. The current and well-known FDA-approved pharmacotherapies for smoking cessation are nicotine patches, available over the counter, and bupropion (Zyban®) tablets, available by prescription. With respect to treating alcohol disorders, as of April 2006, there are four FDA-approved pharmacotherapies for the treatment of alcohol dependence. They are listed here in order of FDA-approval dates: disulfiram (Antabuse®), oral naltrexone (Revia®), acamprosate (Campral®), and, most recently, an extended-release (30-day) injectable suspension formulation of naltrexone (Vivitrol®).

Vivitrol, just recently approved by the FDA for the treatment of alcohol dependence on April 13, 2006, provides clinicians with an innovative way to treat patients with an alcohol disorder. Vivitrol is a once-a-month injection of naltrexone, an opiate antagonist, where one injection provides therapeutic naltrexone plasma concentrations for approximately 30 days. The oral tablet form of naltrexone, approved by the FDA for treating alcohol dependence, has been available for over 10 years (more details are given below), but its daily dosing typically has required high levels of clinician vigilance to ensure that patients don't skip doses or stop taking the medication altogether. That is, taking pills everyday is particularly difficult for this patient population and can ultimately compromise the chances of a good treatment response for a formidable number of patients.[1] Monthly injections relieve patients of the daily decision to take their medicine. This new technology for treating an alcohol disorder also allows clinicians to better determine if their patients are benefiting from naltrexone, because they are assured

that their patients are consistently receiving the medicine. Treatment response is readily observable in the first month of treatment, according to a recent study.[2] Evidence of Vivitrol's effectiveness in reducing heavy drinking comes from a large, national multisite study of two doses of Vivitrol (380mg or 190mg) or placebo added to counseling in 624 alcohol-dependent participants who were given six once-a-month injections over a six-month treatment period. Patients treated with the higher 380mg dose per month (also the FDA-approved dose) demonstrated a greater reduction in heavy drinking than placebo-treated patients who had received counseling and a dummy shot.[2] See the results of the 24-site randomized controlled clinical trial supporting the efficacy and safety of Vivitrol given over six months.[2]

Naltrexone (Revia®) was approved in tablet form (50mg taken daily) by the FDA for the treatment of alcoholism in 1994. Naltrexone is thought to reduce heavy drinking by blocking the "high" that many of those who suffer from an alcohol disorder experience when they consume alcohol.[3] Over 28 randomized controlled trials have been published, with the majority demonstrating naltrexone's safety in alcohol-dependent individuals and its efficacy in reducing heavy drinking and promoting abstinence. Nonetheless, despite these promising clinical trial results, the tablet form of naltrexone has not been widely prescribed.[4] One major factor that has significantly dampened enthusiasm for oral naltrexone is that it is difficult to predict which patients will have trouble taking this medication every day. Poor treatment response is frequently due to medication nonadherence.[1] Vivitrol is an important advance in that the long-acting injection (lasts 30 days) completely bypasses the problems that many patients have in taking medication every day for a chronic disease like an alcohol disorder.

Acamprosate (Campral®) at a 2gm daily dose is another FDA-approved pharmacotherapy for the treatment of alcohol dependence (approved in July 2004). Acamprosate also affects neural reward pathways, although via a different neurobiological remediation than naltrexone. Acamprosate is a putative glutamate modulator agonist and is thought to promote abstinence by alleviating the physical and psychological discomfort (sweating, anxiety, and sleep disturbances) experienced by many alcohol-dependent individuals once they stop drinking. Acamprosate's effectiveness is supported by several randomized, controlled, clinical trials (see meta-analysis by Mann, et al.),[5] and it has been used to treat alcohol use disorders in many European countries as well as Australia for some time now.

Disulfiram has been FDA-approved for the treatment of alcoholism for over 50 years. Disulfiram's mechanism of action is meant to stop all alcohol drinking, and it is entirely different from the other three FDA-approved medications discussed above. Disulfiram blocks an enzyme that is important in fully metabolizing alcohol in the body. This action creates unpleasant physical symptoms (notably nausea and vomiting) if alcohol drinking occurs. Because of its unpleasant consequences when paired with alcohol, this medication has not been widely accepted by patients, and so it is commonly acknowledged to be of limited utility. However, there is evidence that disulfiram can be effective when patients are highly motivated to stop all drinking, or their pill-taking is supervised by a healthcare professional or caring family member.[6]

No medications are FDA-approved at this time for the treatment of stimulants like cocaine dependence. However, recently published data from pilot trials suggest that cocaine use can be reduced by adding a pharmacotherapy to counseling—such as modafinil[7] (FDA-approved treatment for narcolepsy), topiramate[8] (FDA-approved treatment for migraine and seizure disorders), and even disulfiram[9] (FDA-approved treatment for alcoholism). Modafinil is an FDA-approved treatment for narcolepsy, and is thought to blunt cocaine euphoria and increase abstinence via its glutamate-enhancing action. Under the direction of Dr. Charles O'Brien, Charles Dackis and colleagues from the University of Pennsylvania[7] have published data from a sample of 62 cocaine-dependent patients, randomly assigned to 400mg/day of modafinil or placebo for eight weeks, plus all patients also received weekly sessions of cognitive behavioral therapy (CBT).

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In this trial, modafinil-treated patients had significantly more urine drug screens that were negative for cocaine, and these patients were more likely to attain a consecutive period of cocaine abstinence of greater than three weeks. This finding provides exciting preliminary evidence that modafinil could prove to be an effective treatment for cocaine dependence. A larger study is currently underway to confirm these results (*N*=210).

Topiramate is an anticonvulsant medication that facilitates gamma amino butyric acid (GABA) activity and inhibits glutamatergic neurotransmission. Both of these neurotransmitter systems are thought to be involved in the rewarding effects of cocaine. Under the direction of Dr. Charles O'Brien, Kyle Kampman and his colleagues at the University of Pennsylvania have published pilot data on the efficacy of 200mg/day of topiramate versus placebo in 40 cocaine-dependent patients who also received weekly sessions of CBT. Topiramate-treated patients were more likely to be abstinent from cocaine and more likely to sustain three continuous weeks of abstinence than placebo-treated patients who received CBT.[8] Currently, Dr. Kampman and colleagues are conducting a larger randomized placebo-controlled trial of topiramate for the treatment of patients with both cocaine and alcohol dependence (*N*= 200).

In the past decade, scientists have made important progress toward understanding the biological mechanisms underlying alcohol and drug addiction. This knowledge has led to the development of promising phamacotherapies that can be added to counseling in treating addictions. Counseling, or "psychosocial treatments," can refer to a variety of individual and group therapies. Usually counseling does not imply mutual support groups (like Alcoholics and Narcotics Anonymous), but the majority of treatment programs strongly encourage patients to participate in support groups. The efficacy of counseling or psychosocial treatments has been demonstrated in randomized-controlled clinical trials.[10] Nonetheless, relapse rates in some settings remain high, and further investigation of adjunctive pharmacotherapy options is of paramount importance, given our increased knowledge with respect to the neurobiology of addiction. The National Institute on Drug Abuse (NIDA) estimates that alcoholism and drug abuse impose a financial burden on society of about $245.7 billion in a given year.[11] This economic cost must be considered in conjunction with the immeasurable emotional and social burden on addicted individuals and their families. The importance of developing effective treatments is undeniable. Clinical advances, like those discussed above, give hope to the more than 19.4 million Americans (and their families) who suffer from an alcohol or drug disorder.[12]

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